

# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB05/001031

International filing date: 17 March 2005 (17.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB  
Number: 0422880.5  
Filing date: 14 October 2004 (14.10.2004)

Date of receipt at the International Bureau: 09 May 2005 (09.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



INVESTOR IN PEOPLE

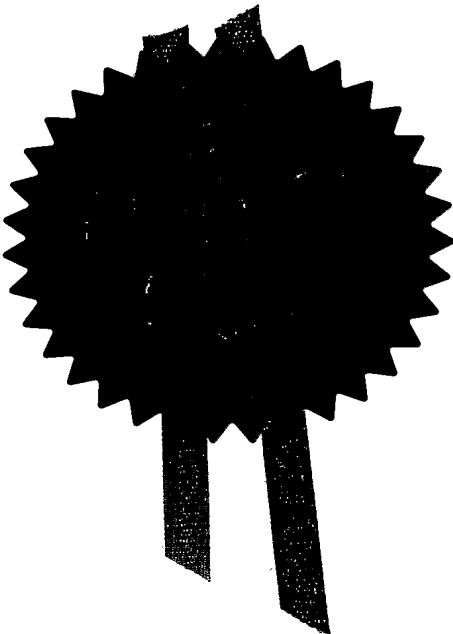
The Patent Office  
Concept House  
Cardiff Road  
Newport  
South Wales  
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

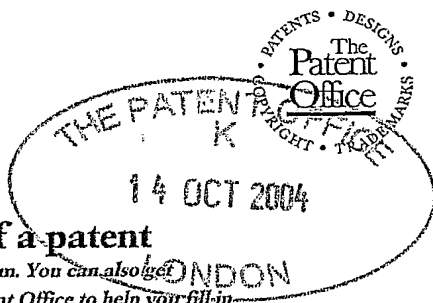
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 19 April 2005





177  
17OCT04 0933882-1 000041  
001/7700 0.00-0422880.5 NONE

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road  
Newport  
South Wales  
NP10 8QQ

14 OCT 2004

1. Your reference	REP077056GB		
2. Patent application number (The Patent Office will fill this part in)	0422880.5		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	Arakis Ltd. Chesterford Research Park Little Chesterford Saffron Walden Essex CB10 1XL		
Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom	08306128001	
4. Title of the invention	The treatment of inflammatory disorders		
5. Name of your agent (if you have one)	Gill Jennings & Every		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Broadgate House 7 Eldon Street London EC2M 7LH		
Patents ADP number (if you know it)	745002 ✓		
6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.	Country	Priority application number (if you know it)	Date of filing (day / month / year)
7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)	Number of earlier UK application		Date of filing (day / month / year)
8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?	YES		
Answer YES if:			
a) any applicant named in part 3 is not an inventor, or			
b) there is an inventor who is not named as an applicant, or			
c) any named applicant is a corporate body.			
Otherwise answer NO (See note d)			



# Patents Form 1/77

Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form

Description 5

Claim(s) 2

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for a preliminary examination and search (Patents Form 9/77)

Request for a substantive examination (Patents Form 10/77)

NO

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

For the applicant

Gill Jennings & Every

Signature

Date 14 October 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward

020 7377 1377

## Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

## Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.



## The treatment of inflammatory disorders

### Field of the invention

This invention relates to the treatment of inflammatory disorders.

### Background

5 Inflammatory diseases remain poorly treated, including many autoimmune diseases, certain IgE mediated (Type I) hypersensitivity reactions, chronic inflammatory disease and skin inflammation. In these patients treatment regimes are often not wholly effective, or are halted due to excessive side effects, allowing the disease to progress. Consequently, there  
10 is a need for drugs which are effective in treating these immune mediated inflammatory conditions, but with substantially fewer side effects.

Immune driven inflammatory events are a significant cause of many chronic inflammatory diseases where prolonged inflammation causes tissue destruction and results in extensive damage and eventual failure of the  
15 effected organ. The cause of these diseases is unknown, so are often called autoimmune, as they appear to originate from an individual's immune system turning on itself. Conditions include those involving multiple organs, such as systemic lupus erythematosus (SLE) and scleroderma. Other types of autoimmune disease can involve specific tissues or organs such as the  
20 musculoskeletal tissue (rheumatoid arthritis, ankylosing spondylitis), gastro-intestinal tract, (Crohn's disease and ulcerative colitis), the central nervous system (Alzheimers, Multiple sclerosis, motor neurone disease, Parkinson's disease and chronic fatigue syndrome), pancreatic beta cells (insulin dependent diabetes mellitus), the adrenal gland (Addison's disease), the  
25 kidney (Goodpasture's syndrome, IgA nephropathy, interstitial nephritis) exocrine glands (Sjogrens syndrome and autoimmune pancreatitis) and skin (psoriasis and atopic dermatitis).

In addition, there are chronic inflammatory diseases whose aetiology is more or less known but whose inflammation is also chronic and unremitting.  
30 These also exhibit massive tissue/organ destruction and include conditions such as osteoarthritis, periodontal disease, diabetic nephropathy, chronic obstructive pulmonary disease, arteriosclerosis, graft versus host disease, chronic pelvic inflammatory disease, endometriosis, chronic hepatitis and tuberculosis. In these diseases the tissue destruction often damages organ



function, resulting in progressive reductions in quality of life and organ failure. These conditions are a major cause of illness in the developing world and poorly treated by current therapies.

IgE mediated (Type I) hypersensitivity reactions result from an inappropriate response to normally non-immunogenic antigens (e.g, pollen and dust-mites). Antigen presentation results in eosinophil infiltration, cytokine burst, inflammation and oedema. These conditions can be triggered by antigens such as mould, dust mites, grass and tree pollen and result in conditions such as rhinitis, asthma, anaphylaxis and dermatitis.

Inflammation of skin structures (dermatitis) is a common set of conditions which include; actinic keratosis, acne rosacea, acne vulgaris, allergic contact dermatitis, angioedema, atopic dermatitis, bullous pemphigoid, cutaneous drug reactions, erythema multiforme, lupus erythematosus, photodermatitis, psoriasis, psoriatic arthritis, scleroderma and urticaria.

These diseases are treated using a wide array of therapies, many of which have very severe side effects.

Current disease modifying treatments (if any), for immune driven conditions, include neutralising antibodies, cytotoxics, corticosteroids, immunosuppressants, antihistamines and antimuscarinics. These treatments are often associated with inconvenient routes of administration and severe side effects leading to compliance issues. Moreover certain drug classes are only effective for certain types of inflammatory diseases; e.g. antihistamines for rhinitis.

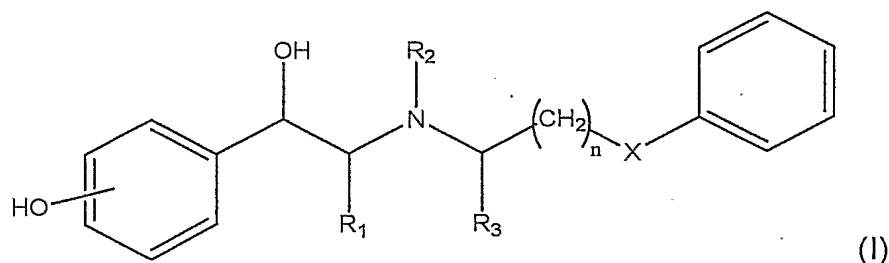
Phenyl substituted beta-amino alcohols (I) are known to have antihypertensive, vasodilator, sympathomimetic, bronchodilator or cardiostimulant activity through agonism and antagonism at alpha and beta adrenoceptors.

### **Summary of invention**

Surprisingly it has been found that phenyl substituted beta-amino alcohols (I) are inhibitors of cytokines and possess anti-inflammatory properties. According to the present invention an inflammatory condition as previously described is treated by the use of (I).

### **Description of Preferred Embodiments**

Phenyl substituted beta-amino alcohols refer to compounds of general formula (I)



5

Wherein:

R<sub>1</sub> may be H or Me

R<sub>2</sub> may be H or alkyl and can be part of a ring with R<sub>3</sub>

10

R<sub>3</sub> may be H or Me or CH<sub>2</sub> (when forming part of a ring with R<sub>2</sub>)

n=0-2

X may be CH<sub>2</sub> or O

The two phenyl groups may be optionally substituted with OH, OMe, halogen, NHCHO, NHSO<sub>2</sub>Me, CONH<sub>2</sub>, SOME

15

It is understood that the invention refers to salts, e.g. the hydrochloride, metabolites and pro-drugs thereof, as well as any diastereomers and enantiomers of (I).

20

A preferred diastereomer or enantiomer of (I) has little or no activity at the  $\alpha$  or  $\beta$  adrenoceptors. This activity may be determined by use of the appropriate in vitro assay.

Compounds of formula (I) include bufenide, butopamine, denopamine, fenoterol, formoterol, ifenprodil, isoxuprine, labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, sulfinalol.

25

According to the invention compounds of formula (I) are used to treat inflammatory diseases including, but not exclusive to, autoimmune diseases involving multiple organs, such as systemic lupus erythematosus (SLE) and scleroderma, specific tissues or organs such as the musculoskeletal tissue (rheumatoid arthritis, ankylosing spondylitis), gastro-intestinal tract, (Crohn's disease and ulcerative colitis), the central nervous system (Alzheimers,

Multiple sclerosis, motor neurone disease, Parkinson's disease and chronic fatigue syndrome), pancreatic beta cells (insulin dependent diabetes mellitus), the adrenal gland (Addison's disease), the kidney (Goodpasture's syndrome, IgA nephropathy, interstitial nephritis) exocrine glands (Sjogrens syndrome and autoimmune pancreatitis) and skin (psoriasis and atopic dermatitis), chronic inflammatory diseases such as osteoarthritis, periodontal disease, diabetic nephropathy, chronic obstructive pulmonary disease, atherosclerosis, graft versus host disease, chronic pelvic inflammatory disease, endometriosis, chronic hepatitis and tuberculosis, IgE mediated (Type I) hypersensitivities such as rhinitis, asthma, anaphylaxis and dermatitis. Dermatitis conditions include; actinic keratosis, acne rosacea, acne vulgaris, allergic contact dermatitis, angioedema, atopic dermatitis, bullous pemphigoid, cutaneous drug reactions, erythema multiforme, lupus erythematosus, photodermatitis, psoriasis, psoriatic arthritis, scleroderma and urticaria.

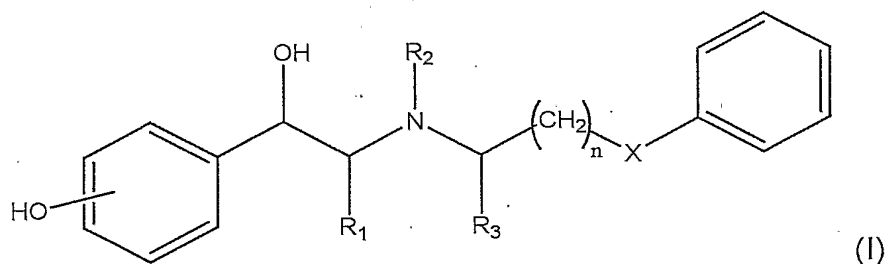
These compounds may be used according to the invention when the patient is also administered or in combination with another therapeutic agent selected from corticosteroids (examples including cortisol, cortisone, hydrocortisone, dihydrocortisone, fludrocortisone, prednisone, prednisolone, deflazacort, flunisolide, beconase, methylprednisolone, triamcinolone, betamethasone, and dexamethasone), disease modifying anti-rheumatic drugs (DMARDs) (examples including, azulfidine, aurothiomalate, bucillamine, chlorambucil, cyclophosphamide, leflunomide, methotrexate, mizoribine, penicillamine and sulphasalazine), immunosuppressants (examples including azathioprine, cyclosporin, mycophenolate) COX inhibitors (examples including aceclofenac, acemetacin, alcofenac, alminoprofen, aloxipirin, amfenac, aminophenazone, antraphenine, aspirin, azapropazone, benorilate, benoxaprofen, benzydamine, butibufen, celecoxib, chlorthenoxacine, choline salicylate, chlometacin, dexketoprofen, diclofenac, diflunisal, emorfazone, epirizole, etodolac, feclobuzone, felbinac, fenbufen, fenclofenac, flurbiprofen, glafenine, hydroxylethyl salicylate, ibuprofen, indometacin, indoprofen, ketoprofen, ketorolac, lactyl phenetidin, loxoprofen, mefenamic acid, metamizole, mofebutazone, mofezolac, nabumetone, naproxen, nifenazone, oxametacin, phenacetin, pipebuzone, pranoprofen, propyphenazone, proquazone, rofecoxib, salicylamide, salsalate, sulindac, suprofen, tiaramide,

tinoridine, tolfenamic acid, zomepirac) neutralising antibodies (examples including, etanercept and infliximab), antibiotics (examples including, doxycycline and minocycline).

5 Any suitable route of administration can be used. For example, any of oral, topical, parenteralocular, rectal, vaginal, inhalation, buccal, sublingual and intranasal delivery routes may be suitable. The dose of the active agent will depend on the nature and degree of the condition, the age and condition of the patient and other factors known to those skilled in the art. A typical dose is 10-100 mg given one to three times per day.

## Claims

1. Use of compounds of general formula (I) for the treatment or prevention of a condition associated with T-cell proliferation or that is mediated by pro-inflammatory cytokines



Wherein:

- 10  $R_1$  may be H or Me  
 $R_2$  may be H or alkyl and can be part of a ring with  $R_3$   
 $R_3$  may be H or Me or  $CH_2$  (when forming part of a ring with  $R_2$ )  
 $n=0-2$   
 $X$  may be  $CH_2$  or O
- 15 The two phenyl groups may be optionally substituted with OH, OMe, halogen,  $NHCHO$ ,  $NHSO_2Me$ ,  $CONH_2$ ,  $SOMe$ .
2. Use according to claim 1 wherein the compound is selected from bufeniode, butopamine, denopamine, fenoterol, formoterol, ifenprodil, isoxuprine, labetalol, medroxalol, mesuprine, nyldrin, protokylol, ritodrine,
- 20 salmefamol, sulfinalol.
3. Use according to claim 1 or 2 wherein the condition is a chronic degenerative disease such as rheumatoid arthritis, osteoarthritis or osteoporosis.
4. Use according to claim 1 or 2 wherein the condition is a chronic
- 25 demyelinating disease such as multiple sclerosis.
5. Use according to claim 1 or 2 wherein the condition is a respiratory disease such as asthma or chronic obstructive pulmonary disease.

6. Use according to claim 1 or 2 wherein the condition is an inflammatory bowel disease (IBD) such as ulcerative colitis or Crohn's disease.
7. Use according to claim 1 or 2 wherein the condition is a dermatological condition such as psoriasis, scleroderma or atopic dermatitis.
8. Use according to claim 1 or 2 wherein the condition is a dental disease such as periodontal disease or gingivitis.
9. Use according to claim 1 or 2, wherein the condition is diabetic nephropathy, lupus nephritis, IgA nephropathy or glomerulonephritis.
10. Use according to claim 1 or 2 wherein the condition is systemic lupus erythematosus (SLE).
11. Use according to claim 1 or 2 wherein the condition is graft vs host disease.
12. Use according to any preceding claim wherein the patient is also administered another therapeutic agent selected from corticosteroids, cytotoxics, antibiotics, immunosuppressants and COX inhibitors.
13. Use according to claim 12 wherein compound (I) and said another agent are provided in combination.

